El ct d Claims

The Examiner acknowledges applicants' election of Group I claims. However, although the Examiner defines Group I as consisting of claims 1-30 and 56, the Examiner next states that claims 11-12, 14-16, 19, and 24-55 are withdrawn from further consideration as being drawn to non-elected inventions, and that claims 1-10, 13, 17-18, 20-23 and 56 are currently under consideration. Since claims 1-30 and 56 are all drawn to a method of inhibiting an unwanted angiogenic condition (and claims 31-55 are drawn to an immunogen), applicant assumes in this response that the Examiner meant to consider claims 1-30 and 56 in the October 19, 2001 Office Action.

P nding Claims

Applicants assume for the reasons stated above under "Elected Claims" that claims 31-55 have been withdrawn from consideration by the Examiner as being drawn to non-elected inventions, and that claims 1-30 and 56 are now under examination in the subject application.

CLAIM OBJECTIONS

The Examiner objected to claims 20-23 for minor grammatical errors in reciting "wherein the a molecule." Applicants have amended claims 20-23 to correct these grammatical errors, and therefore respectfully request the Examiner to withdraw this objection.

CLAIM REJECTIONS – 35 U.S.C. 112

The Examiner rejects claims 1-10 , 13, 17-18, 20-23 and 56 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner contends claims 1-10 , 13, 17-18, 20-23 and 56 are vague because they recite "treating" in claims 1 and 56. Applicants have amended these claims as suggested by the Examiner to recite "comprising administering to the mammal an effective amount...." Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of these claims.

The Examiner also rejects claims 1 and 17-18 as vague for reciting "the immunogen is expressed on an antigen presenting cell not native to the mammal" in claim 17. The Examiner alleges that it is not clear which product, the antigen presenting cell or the immunogen, is actually "non-native" to the mammal. Applicants have amended claim 17 to clarify that the APC is foreign. Consequently, claim 18 has also been clarified due to its dependence on claim 17. As defined in the specification (first paragraph, page 9-11 and 18), however, the immunogens and the adjuvants, including APCs, of the invention may be native or foreign to the mammal being treated.

The Examiner further rejects claim 13 for reciting "substantially." According to the Examiner, the term "substantially" is not defined by the claim, and the specification does not provide a standard for ascertaining the degree of purity required. Although the claims must describe subject matter of the invention with a reasonable degree of clarity and particularity, definiteness of claim language must be analyzed not in a vacuum, but in light of the content of the disclosure, prior art teachings, and claim interpretation that would be understood by one possessing ordinary skill in the art at the time the invention was made (MPEP 2173). It is clear from the specification that in a preferred embodiment, "substantially purified" would be purified enough so that it is still an immunogen that would cause an immune response against an angiogenic molecule. Nevertheless, in the interest of furthering prosecution, Applicants have deleted the term "substantially." Claim 7, however, recites the term "immunogen" without limitation, thereby encompassing varying degrees of purification of such immunogens, provided that such immunogens elicit an immune response in a mammal.

In view of the above amendments and discussion, applicant maintains that the

claims particularly point out and distinctly claim the subject matter which applicant regards as the invention. Accordingly, applicant respectfully requests that the rejections under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

Rejection Under 35 U.S.C. §112, First Paragraph

The Examiner rejects claims 1-10, 13, 17-18, 20-23 and 56 under 35 U.S.C. §112, first paragraph, asserting that these claims contain subject matter not described in the specification in a way as to enable a person skilled in the art to use the invention. Essentially, the Examiner alleges that in the present case, undue experimentation would be required to practice the claimed invention because the claims are broadly drawn, the art is unpredictable, and the working examples and guidance are limited. The Examiner therefore concludes that, based on these factors considered in determining whether undue experimentation is required, chosen from the factors summarized in *Ex parte Forman*, that use of the invention as claimed is not enabled.

Applicants maintain that the present application teaches one skilled in the art of the scope of the methods of the invention. While experimentation may be required, it would be routine. The law as set forth in *In re Wands* and in numerous other cases provides that "enablement is not precluded by the necessity of some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" Following the instructions provided by applicants, it is a simple and routine matter for one skilled in the art to perform the invention as claimed.

The Examiner states that the claims are not enabled because the specification allegedly does not provide guidance and objective evidence that the claimed method would predictably inhibit an unwanted angiogenic condition *in vivo* by treatment with an effective amount of an immunogen. In particular, the Examiner contends that there is no objective evidence that administration of the immunogen *in vivo* would elicit any immune response.

According to the Examiner, those having skill in the art of cancer vaccines recognize that active specific immunotherapy may hold promise for the future, but is rather unpredictable. The Examiner cites the following three references to demonstrate the unpredictability of the art: Spitler, Bellone et al. and Gura.

The Examiner cites Spitler to show that those with skill in the art of cancer vaccines most likely believe that cancer vaccines do not work. However, the gist of the Spitler reference is that cancer vaccines are on the cusp of commercial development (see page 2, first full paragraph of Spitler). Spitler counters the initial observation that "cancer vaccines don't work" with an analogy to interferon, stating at the end of the article, "Now that the active components of the vaccines have been identified and purified, we are approaching the stage in technology where the interferons were at the beginning of the 1980s. The decade of the vaccines may finally have arrived!" Spitler also states on page 2, first column, that "almost everyone working in this field has had the experience of seeing a dramatic regression of metastatic disease following vaccine therapy." (page 2, first column of Spitler). The consistency, rather than the unpredictability, of the art is further underscored by Spitler's statement that "many groups are approaching vaccine therapy for cancer using defined, purified antigens as described in the abstracts of this issue of Cancer Biotherapy." In view of these statements in Spitler, applicants maintain that instead of demonstrating the unpredictability of the art of cancer vaccine therapy, Spitler demonstrates the feasibility of this new therapy, and actually provides objective evidence regarding administration of an immunogen *in vivo* that elicits an immune response useful in cancer therapy.

Next, the Examiner cites Bellone et al. as summarizing the current state of the art of peptide immunotherapy, including clinical trials, where "there is usually a poor correlation between induction of specific T-cells and the clinical responses." (Bellone et al., p. 457, 2nd col.). Further, the Examiner notes that Bellone et al. teach the disadvantages of peptide cancer immunotherapy in that (1) there is no direct evidence

for a role in tumor rejection, (2) the therapy is applicable to few patients, (3) there is a risk of generating tumor escape mutants, and (4) a risk of autoimmune reactions (Bellone et al., page 461, Box 1).

On page 451, in the Concluding Remarks, Bellone et al. notes that (1) the results of Phase I clinical trials with synthetic peptides that correspond to defined tumor antigens have demonstrated the feasibility of their use as vaccines. Further, the Bellone et al. article states that recent clinical responses of cancer patients treated with dendritic cells pulsed with autologous tumor lysates strongly support the use of natural tumor peptides in cancer immunotherapy. On page 461, Bellone et al. state that self-antigens should already have determined a selective tolerance during ontogeny and life. Further, Bellone et al. state that as yet there is no evidence of autoimmunity in animals immunized with naturally processed tumor peptides. Finally, as the Examiner notes, Bellone et al. is directed to tumor antigens, not angiogenic immunogenic molecules, and therefore is not an appropriate reference to show the state of the art relating to the present invention.

In citing Gura, the Examiner contends that the treatment of cancer is at most unpredictable, and reiterates Gura's discussion of the potential shortcomings of potential anti-cancer agents including extrapolating from in vitro to in vivo protocols, the problems of drug testing in knockout mice, particularly strains which have tumor suppressor gene knockouts, and the problems of clonogenic assays. Gura's discussion, however, focuses on identifying specific drugs for specific tumors, whereas the present invention applies to any tumor or angiogenic condition. The cancer screening methods discussed by Gura are most likely different from those that would be used for angiogenic vaccines of the present invention. For example, the xenograft assay is used to test drugs for specific types of cancers (see box on page 1042). On page 1042 (second to last paragraph), Gura states that researchers are now classifying cells in their screening panels according to the types of genetic defects the cells carry, and will eventually be able to match each individual's tumor cell makeup with a drug, thereby provide a promising new approach to cancer drug screening. Gura also quotes

a pharmaceutical executive as saying that "the future of cancer drug screening is turning almost exclusively toward defining molecular targets." An angiogenesis inhibitor, however, would not be screened in this way because it would be used for any cancer, not a specific tumor type, or any angiogenic condition. Accordingly, the Examiner's contention that model drug discovery systems for cancer are not predictive is inapplicable to the present invention.

Applicant maintains that, for the reasons delineated above, the findings of the cited references do not demonstrate the unpredictability of the art relating to present invention. Instead, these references underscore the feasibility of cancer vaccine therapy, and even provide objective evidence and guidance regarding administration of an immunogen that elicits an immune response.

The Examiner contends that, in connection with claims 1, 17 and 18, there is insufficient evidence that the method will predictably treat an unwanted angiogenic condition wherein the immunogen is expressed on an antigen-presenting cell (APC) not native to the mammal. According to the Examiner, it is not clear in the specification if the APC is foreign or if the immunogen is foreign. The Examiner contends that if the APC is foreign, there is not enough evidence in the specification that the host immune system response will be directed against native angiogenic moleules and not the foreign cells themselves. Secondly, the Examiner contends that if the immunogen is foreign there is not enough guidance in the specification that the immune response will be directed against native angiogenic molecules and not the foreign peptide.

Applicants have amended claim 17 to clarify that the APC is foreign, although the specification does not limit the APC or the immunogen to being foreign or native. If the immunogen is foreign, it is clear from the specification that it would be chosen or synthesized to be in a form that would elicit an immune response against angiogenic molecules. The question is whether the disclosure is sufficient to enable those skilled in the art to practice the claimed invention, hence the specification need not disclose what is known in the art. It is known in the art that foreign (i.e., including allogeneic) antigens

would prime a CTL response against the native as well as foreign antigens. Bellone, cited by the examiner in this rejection, states that "Importantly, CTLs from a melanoma patient, induced with naturally processed tumor peptides from an allogeneic HLA matched melanoma, killl the autologous tumor. Indeed, strong evidence is now available on CTL priming across allogeneic barriers," citing Huang et al. (1994) Science 264, 961-965, and Toes, et al. (1996) Cancer Res. 56:3782-3787. Accordingly, the APCs may be foreign or native to the host receiving treatment.

Furthermore, the APCs of the invention may be native or foreign, and for example, may be engineered to express the immunogen (see specification, pages 10-11 and 18, second paragraph). It is established that "...a patent need not teach, and preferably omits, what is well known in the art" (Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 at 94 (C.A.F.C. 1986). It is well known in the art that APCs may be used as adjuvants. See, for example, U.S. Patent Nos. 5,580,563 and 5,788,963, cited in the Background of the Invention on page 2 of the present application. It is therefore desirable to be able to use dendritic cells, a form of APCs to process and present protein antigens as a means of modulating an individual's immune response, and in particular to activate an individual's T cells in connection with the treatment or prevention of disease. (Steinman et al., U.S. Patent No. 6,274,378). "Because of the potent activity of dendritic cells to activate T cells, the art, e.g. Flanand et al., Env. J. Immunol., 24:605-610, 1994, has accepted the characterization of dendritic cells as "nature's adjuvant'." (Quoted from Steinman et al., U.S. Patent No. 6,274,378). Therefore, at the time of the invention it was known that the host immune system is capable of directing a response against native angiogenic molecules and not merely, as speculated by the Examiner, the foreign APCs themselves.

The Examiner notes that the U.S. Patent No. 5,597,563, cited in the specification, is concerned with inducing antigen-specific immune tolerance and not eliciting an immune response against an angiogenic molecule. Applicants cited this patent for no other reason than to provide a background and examples of antigen presenting cells, not to provide examples or data for eliciting an immune response against an angiogenic

molecule. Other examples of antigen presenting cells are cited in the Background of the Invention, p.2, as noted above (U.S. Patent Nos. 5,580,563 and 5,788,963).

The Examiner further contends that the disclosure does not provide working examples wherein all of the steps required to practice the method are employed, and that such lack of working examples is given added weight in cases involving an unpredictable and undeveloped art such as the treatment of cancer.

The determination whether "undue experimentation" is needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all factual considerations (MPEP § 2164.08, §2164.05(a), §2164.05(b), §2164.03, §2164.02, and 2164.06). As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The present specification does provide a protocol (Experimental Examples, pp. 22-23) for practicing the claims: i.e., inhibiting (see Experimental Results) an unwanted angiogenic condition (tumor metastases) in a mammal (mouse) in need thereof comprising treating the mammal with an effective amount of an immunogen (vaccination of the mice with dendritic cells pulsed with Flk-1 and alkaline phosphatase) that causes an immune response against a molecule that induces angiogenesis (Flk-1 levels are upregulated by VEGF, see Background, p.7 of specification) in the mammal. Therefore, the disclosure does provide working examples employing all of the steps required to practice the method.

Furthermore, it has been held that it is unimportant how a specification teaches the invention, whether by the use of illustrative examples or by broad descriptive terminology. A specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first

paragraph of 35 USC 112 unless there is reason to doubt the objective truth of the statements relied upon therein for enabling support.

In conclusion, in the case of the present invention no undue experimentation would be required to make and use the invention as claimed. The *Forman* factors raised by the examiner, i.e., the breadth of the claims, the guidance provided, working examples, and the predictability of the art, have been discussed above. The Examiner's cited references do not prove that undue experimentation is necessary, and instead provide guidance for a skilled practitioner in the art to inhibit an unwanted angiogenic condition in a mammal using an immunogen that causes an immune response against an angiogenic molecule. The state of the prior art is such that isolating or making immunogens and administering such immunogens to mammals could be carried out by one skilled in the art with applicants' disclosure. The relative skill of the art is high, and use of immunogens to generate an immune response is not unpredictable. The amount of experimentation is minimal because the specification provides methods and working examples. Ample guidance is presented by applicants as to how to make the claimed immunogens and how to carry out the claimed methods.

In view of the above discussion, all embodiments of the present invention are fully enabled and allow the skilled artisan to practice the claimed invention. Therefore, applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Additional Rejection Under 35 U.S.C. 112, first paragraph

The Examiner further rejected the pending claims under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the method as broadly claimed. The Examiner contends that "one cannot extrapolate the teachings of the specification with the scope of the claims." According to the Examiner, the claims include eliciting an immune response with an "unmodified" immunogen, including native immunogens or "self" proteins, which would not easily elicit an immune

response because of immune tolerance of "self" proteins.

Claim 1 provides for the use of an effective amount of an immunogen that causes an immune response against an angiogenic molecule in the mammal. According to the claim, the immunogen, whether native or foreign to the host mammal, must be able to elicit an immune response to an angiogenic molecule. Since most native immunogens would not elicit an immune response in their native hosts, it is understood from the specification (pp 9-11) and dependent claims (such as claim 7) that native immunogen of the invention would need to be modified to improve immunogenicity. However, in certain instances, perhaps if a native immunogen is expressed in abundance, i.e., by a recombinant antigen presenting cell, the host immune system may recognize the native immunogen as foreign and launch an immune response. Accordingly the pending claims are within the scope of the teachings of the specification, even if they include native immunogens or "self" proteins.

Since the specification is enabling for the claims as discussed above, applicants respectfully request the Examiner to reconsider and withdraw the rejection of the pending claims under 35 U.S.C. 112, first paragraph.

Rejection Under 35 U.S.C. § 102(e)

The Examiner rejected the pending claims under 35 U.S.C. 102(e) as being anticipated by Nacy et al. The Examiner contends that Nacy et al. teach a method of inhibiting an unwanted angiogenic condition including tumors, arthritis, macular degeneration, and psoriasis in a mammal or human in need thereof comprising treating the mammal with an effective amount of an immunogen, native or foreign, such that the immunogen causes an immune response against a molecule that induces angiogenesis in the mammal.

A reference must disclose each and every element of the claim to be considered

anticipatory prior art. There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention.

Nacy et al. is directed to a method for inhibiting growth factors in cancer cells and tissues for treating cancer and hyperproliferative disorders. Unlike applicants' invention, Nacy et al. does not disclose the use of immunogens to cause an immune response against any angiogenic molecule. Instead, Nacy et al.'s disclosure of angiogenesis factors is limited to circulating growth factors (col. 1 lines 61-63). Applicants' definition of angiogenesis factors is not limited to growth factors, but includes any angiogenic molecules such as flt-1, flk-1, KDR, angiopoietin 1 and 2, TIE-1 and TIE-1/TEK, and VE-Cadherin 1 and 2. Furthermore, Nacy et al. specifically defines its immunogenic compositions as "growth factor-containing compositions." Applicants' invention includes any immunogen, not necessarily an angiogenic molecule at all, that stimulates the immune system against an angiogenic molecule. Nacy et al. disclose merely growth factors related to cancer and angiogenesis and used as immunogens. Nacy et al. do not disclose the specific immunogens of the present application. Additionally, there is no mention of recombinant immunogens, or of anti-idiotypic antibodies. Accordingly, Nacy et al. does not disclose each and every element of applicants' claimed invention, and cannot be considered anticipatory prior art. At most, Nacy et al. is an invitation to experiment. Accordingly, an anticipation rejection under 35 U.S.C. § 102(e) is improper and applicants request reconsideration and withdrawal of this rejection.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all outstanding objections and rejections.

If a telephone conference would be of assistance in furthering the prosecution of the application, Applicant's undersigned attorney requests that he be contacted at the telephone number provided below.

If additional fees are deemed necessary for the filing of this Amendment, authorization is hereby given to charge any such fees to Deposit Account No. 11-0171. Prompt and favorable consideration of this Amendment is respectfully requested.

Respectfully submitted,

Thomas C. Gallagher
Reg. No. 37,066

ImClone Systems Incorporated
180 Varick Street
New York, N.Y. 10014
(646) 638-5031

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